



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

|  |                              |  |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
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| (51) International Patent Classification 7 :<br>C12N 15/12, C07K 14/47, A61K 38/17,<br>G01N 33/53, C12Q 1/68, C12N 15/62,<br>C07K 16/18  |                              | A2   | (11) International Publication Number: WO 00/53758 |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| (21) International Application Number: PCT/US00/05841  |                              | (43) International Publication Date: 14 September 2000 (14.09.00)  |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| (22) International Filing Date: 2 March 2000 (02.03.00)  |                              | (71) Applicant (for all designated States except US): GENENTECH, INC. [US/US]; 1 DNA Way, South San Francisco, CA 94080-4990 (US).   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| (30) Priority Data:  |                              | (72) Inventors; and  |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| <table border="0"> <tr><td>PCT/US99/05028</td><td>8 March 1999 (08.03.99)</td><td>US</td></tr> <tr><td>60/123,618</td><td>10 March 1999 (10.03.99)</td><td>US</td></tr> <tr><td>60/123,957</td><td>12 March 1999 (12.03.99)</td><td>US</td></tr> <tr><td>60/125,775</td><td>23 March 1999 (23.03.99)</td><td>US</td></tr> <tr><td>60/128,849</td><td>12 April 1999 (12.04.99)</td><td>US</td></tr> <tr><td>PCT/US99/08615</td><td>20 April 1999 (20.04.99)</td><td>US</td></tr> <tr><td>60/131,445</td><td>28 April 1999 (28.04.99)</td><td>US</td></tr> <tr><td>60/132,371</td><td>4 May 1999 (04.05.99)</td><td>US</td></tr> <tr><td>60/134,287</td><td>14 May 1999 (14.05.99)</td><td>US</td></tr> <tr><td>PCT/US99/12252</td><td>2 June 1999 (02.06.99)</td><td>US</td></tr> <tr><td>60/141,037</td><td>23 June 1999 (23.06.99)</td><td>US</td></tr> <tr><td>60/144,758</td><td>20 July 1999 (20.07.99)</td><td>US</td></tr> <tr><td>60/145,698</td><td>26 July 1999 (26.07.99)</td><td>US</td></tr> <tr><td>60/146,222</td><td>28 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<tr><td>PCT/US99/28551</td><td>2 December 1999 (02.12.99)</td><td>US</td></tr> <tr><td>PCT/US99/28564</td><td>2 December 1999 (02.12.99)</td><td>US</td></tr> <tr><td>PCT/US99/28565</td><td>2 December 1999 (02.12.99)</td><td>US</td></tr> <tr><td>PCT/US99/30095</td><td>16 December 1999 (16.12.99)</td><td>US</td></tr> <tr><td>PCT/US99/30999</td><td>20 December 1999 (20.12.99)</td><td>US</td></tr> <tr><td>PCT/US99/31274</td><td>30 December 1999 (30.12.99)</td><td>US</td></tr> <tr><td>PCT/US00/00219</td><td>5 January 2000 (05.01.00)</td><td>US</td></tr> <tr><td>PCT/US00/00277</td><td>6 January 2000 (06.01.00)</td><td>US</td></tr> <tr><td>PCT/US00/00376</td><td>6 January 2000 (06.01.00)</td><td>US</td></tr> <tr><td>PCT/US00/03565</td><td>11 February 2000 (11.02.00)</td><td>US</td></tr> <tr><td>PCT/US00/04341</td><td>18 February 2000 (18.02.00)</td><td>US</td></tr> <tr><td>PCT/US00/04342</td><td>18 February 2000 (18.02.00)</td><td>US</td></tr> <tr><td>PCT/US00/04414</td><td>22 February 2000 (22.02.00)</td><td>US</td></tr> </table> |                              | PCT/US99/05028   | 8 March 1999 (08.03.99)                            | US | 60/123,618 | 10 March 1999 (10.03.99) | US | 60/123,957 | 12 March 1999 (12.03.99) | US | 60/125,775 | 23 March 1999 (23.03.99) | US | 60/128,849 | 12 April 1999 (12.04.99) | US | PCT/US99/08615 | 20 April 1999 (20.04.99) | US | 60/131,445 | 28 April 1999 (28.04.99) | US | 60/132,371 | 4 May 1999 (04.05.99) | US | 60/134,287 | 14 May 1999 (14.05.99) | US | PCT/US99/12252 | 2 June 1999 (02.06.99) | US | 60/141,037 | 23 June 1999 (23.06.99) | US | 60/144,758 | 20 July 1999 (20.07.99) | US | 60/145,698 | 26 July 1999 (26.07.99) | US | 60/146,222 | 28 July 1999 (28.07.99) | US | PCT/US99/20111 | 1 September 1999 (01.09.99) | US | PCT/US99/20594 | 8 September 1999 (08.09.99) | US | PCT/US99/20944 | 13 September 1999 (13.09.99) | US | PCT/US99/21090 | 15 September 1999 (15.09.99) | US | PCT/US99/21547 | 15 September 1999 (15.09.99) | US | 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2000 (22.02.00) | US | (75) Inventors/Applicants (for US only): ASHKENAZI, Avi, J. 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| PCT/US99/05028   | 8 March 1999 (08.03.99)      | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
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| PCT/US99/08615   | 20 April 1999 (20.04.99)     | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
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| PCT/US99/12252   | 2 June 1999 (02.06.99)       | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| 60/141,037   | 23 June 1999 (23.06.99)      | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| 60/144,758   | 20 July 1999 (20.07.99)      | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| 60/145,698   | 26 July 1999 (26.07.99)      | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| 60/146,222   | 28 July 1999 (28.07.99)      | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| PCT/US99/20111   | 1 September 1999 (01.09.99)  | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| PCT/US99/20594   | 8 September 1999 (08.09.99)  | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| PCT/US99/20944   | 13 September 1999 (13.09.99) | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| PCT/US99/21090   | 15 September 1999 (15.09.99) | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| PCT/US99/21547   | 15 September 1999 (15.09.99) | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| PCT/US99/23089   | 5 October 1999 (05.10.99)    | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| 60/162,506   | 29 October 1999 (29.10.99)   | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| PCT/US99/28214   | 29 November 1999 (29.11.99)  | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| PCT/US99/28313   | 30 November 1999 (30.11.99)  | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| PCT/US99/28409   | 30 November 1999 (30.11.99)  | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| PCT/US99/28301   | 1 December 1999 (01.12.99)   | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| PCT/US99/28634   | 1 December 1999 (01.12.99)   | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| PCT/US99/28551   | 2 December 1999 (02.12.99)   | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| PCT/US99/28564   | 2 December 1999 (02.12.99)   | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| PCT/US99/28565   | 2 December 1999 (02.12.99)   | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| PCT/US99/30095   | 16 December 1999 (16.12.99)  | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| PCT/US99/30999   | 20 December 1999 (20.12.99)  | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| PCT/US99/31274   | 30 December 1999 (30.12.99)  | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| PCT/US00/00219   | 5 January 2000 (05.01.00)    | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| PCT/US00/00277   | 6 January 2000 (06.01.00)    | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| PCT/US00/00376   | 6 January 2000 (06.01.00)    | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| PCT/US00/03565   | 11 February 2000 (11.02.00)  | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| PCT/US00/04341   | 18 February 2000 (18.02.00)  | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| PCT/US00/04342   | 18 February 2000 (18.02.00)  | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
| PCT/US00/04414   | 22 February 2000 (22.02.00)  | US   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
|  |                              | (74) Agents: SVOBODA, Craig, G. et al.; Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080-4990 (US).   |  |    |            |                          |    |            |                          |    |            |                          |    |            |                          |    |                |                          |    |            |                          |    |            |                       |    |            |                        |    |                |                        |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |                |                             |    |                |                             |    |                |                              |    |                |                              |    |                |                              |    |                |                           |    |            |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                            |    |                |                             |    |                |                             |    |                |                             |    |                |                           |    |                |                           |    |                |                           |    |                |                             |    |                |                             |    |                |                             |    |                |                             |    |   |  |
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(54) Title: COMPOSITIONS AND METHODS FOR THE TREATMENT OF IMMUNE RELATED DISEASES

## (57) Abstract

The present invention relates to a composition containing novel proteins and methods for the diagnosis and treatment of immune related diseases.

surface of an antigen presenting cell and CD28 and CTLA-4 molecules expressed on the T cell surface effect cell activation. Activated T cells express an increased number of cellular adhesion molecules, such as ICAM-1, integrins, VLA-4, LFA-1, CD56, etc.

T-cell proliferation in a mixed lymphocyte culture or mixed lymphocyte reaction (MLR) is an established indication of the ability of a compound to stimulate the immune system. In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neurophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994. John Wiley & Sons, Inc.

Immune related diseases can be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

#### Summary of the Invention

The present invention concerns compositions and methods for the diagnosis and treatment of immune related disease in mammals, including humans. The present invention is based on the identification of proteins (including agonist and antagonist antibodies) which either stimulate or inhibit the immune response in mammals. Immune related diseases can be treated by suppressing or enhancing the immune response. Molecules that enhance the immune response stimulate or potentiate the immune response to an antigen. Molecules which stimulate the immune response can be used therapeutically where enhancement of the immune response would be beneficial. Such stimulatory molecules can also be inhibited where suppression of the immune response would be of value.

Neutralizing antibodies are examples of molecules that inhibit molecules having immune stimulatory activity and which would be beneficial in the treatment of immune related and inflammatory diseases. Molecules which inhibit the immune response can also be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

Accordingly, the PRO polypeptides and anti-PRO antibodies and fragments thereof are useful for the diagnosis and/or treatment (including prevention) of immune related diseases. Antibodies which bind to stimulatory proteins are useful to suppress the immune system and the immune response. Antibodies which bind to inhibitory proteins are useful to stimulate the immune system and the immune response. The PRO polypeptides and anti-PRO antibodies also useful to prepare medicines and medicaments for the treatment of immune related and inflammatory diseases.

In one embodiment, the invention provides for isolated nucleic acid molecules comprising nucleotide sequences that encodes a PRO polypeptide.

In one aspect, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about

Figure 126 shows the native sequence PRO4430 polypeptide UNQ1947 (SEQ ID NO:295).

Figure 127 shows DNA98853-1739 (SEQ ID NO:296).

Figure 128 shows the native sequence PRO5727 polypeptide UNQ2448 (SEQ ID NO:297).

## Detailed Description of the Preferred Embodiments

### I. Definitions

The terms "PRO polypeptide(s)" and "PRO" as used herein and when immediately followed by a numerical designation refer to various polypeptides, wherein the complete designation (*i.e.*, "PRO/number" or more particularly, PRO200, PRO204, PRO212, PRO216, PRO226, PRO240, PRO235, PRO245, PRO172, PRO273, PRO272, PRO332, PRO526, PRO701, PRO361, PRO362, PRO363, PRO364, PRO356, PRO531, PRO533, PRO1083, PRO865, PRO770, PRO769, PRO788, PRO1114, PRO1007, PRO1184, PRO1031, PRO1346, PRO1155, PRO1250, PRO1312, PRO1192, PRO1246, PRO1283, PRO1195, PRO1343, PRO1418, PRO1387, PRO1410, PRO1917, PRO1868, PRO205, PRO21, PRO269, PRO344, PRO333, PRO381, PRO720, PRO866, PRO840, PRO982, PRO836, PRO1159, PRO1358, PRO1325, PRO1338, PRO1434, PRO4333, PRO4302, PRO4430 or PRO5727) refers to particular polypeptide sequences as described herein. The terms "PRO/number polypeptide" and "PRO/number" wherein the term "number" is provided as an actual numerical designation (*e.g.*, as described above) as used herein encompass native sequence polypeptides and polypeptide variants (which are further defined herein). The PRO polypeptides described herein may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods.

A "native sequence PRO polypeptide(s)" comprises a polypeptide having the same amino acid sequence as the corresponding PRO polypeptide derived from nature. Such native sequence PRO/number polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence PRO polypeptide(s)" specifically encompasses naturally-occurring truncated or secreted forms of the specific PRO/number polypeptide (*e.g.*, an extracellular domain sequence), naturally-occurring variant forms (*e.g.*, alternatively spliced forms) and naturally-occurring allelic variants of the polypeptide. In various embodiments of the invention, the native sequence PRO polypeptides disclosed herein are mature or full-length native sequence polypeptides comprising the full-length amino acids sequences shown in the accompanying figures. Start and stop codons are shown in bold font and underlined in the figures. However, while the PRO/number polypeptides disclosed in the accompanying figures are shown to begin with methionine residues designated herein as amino acid position 1 in the figures, it is conceivable and possible that other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the PRO polypeptides.

The "PRO polypeptide(s) extracellular domain" or "ECD" refers to a form of the said polypeptide which is essentially free of the transmembrane and cytoplasmic domains. Ordinarily, a PRO polypeptide ECD will have less than 1% of such transmembrane and/or cytoplasmic domains and preferably, will have less than 0.5% of such domains. It will be understood that any transmembrane domains identified for the PRO polypeptides of the present invention are identified pursuant to criteria routinely employed in the art for identifying that type of hydrophobic domain. The exact boundaries of a transmembrane domain may vary but most likely by no more than about 5 amino acids at either end of the domain as initially identified herein.

Figure 128

MDCQENEYWDQWGRCVTCQRCGPGQELSKDCGYGEGGDAYCTACPPRRYKSSWGHHRQC  
SCITCAVINRVQKVNCTATSNVAVCGDCLPRFYRKTRIGGLQDQECIPCTKQTPTSEVQC  
AFQLSLVEADAPTVPPEATLVALVSSLLVVFTLAFLGLFFLYCKQFFNRHCQRVTGGL  
LQFEADKTAKESLFPVPPSKETSAESQVSENIQTQPLNPILEDDCSSTSGFPTQESF  
TMACTSESHSEWVHSPIECTELDLQKFSSSASYTGAETLGGNTVESTGDRLELNVPFE  
VPSF